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Effects of Dexamethasone and High Terrestrial Altitude
on Cognitive Performance and Affect

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Running Head: Dexamethasone & Performance

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(3. patient + corticosteroid)

Abstract

This study examined the effects of dexamethasone and exposure to high terrestrial altitude on cognitive performance, affect, and personality traits. Cognitive performance was evaluated by 5 cognitive tasks, affect was evaluated by the Clyde Mood Scale and the Multiple Affect Adjective Check List, and personality traits were examined using the Minnesota Multiphasic Personality Inventory. Sixteen healthy young men received either dexamethasone (4 mg every 6 h) or placebo for 48 h prior to and after ascent to 4300 m. Subjects treated with dexamethasone correctly performed more computer interaction and addition problems than did placebo-treated subjects. They also were less sleepy, dizzy, depressed, and anxious than placebo-treated subjects on the first day at altitude. No adverse effects on cognitive performance, affect, or personality traits were noted after dexamethasone was discontinued on the third day at altitude. Results indicate that dexamethasone at the present dose positively influences cognitive performance and mood states at altitude, but it does not affect personality traits. *Keywords:*

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Effects of Dexamethasone and High Terrestrial Altitude
on Cognitive Performance and Affect

The majority of persons rapidly ascending to terrestrial elevations exceeding 4000 m experience symptoms of headache, nausea, vomiting, lassitude, and sleep disturbances (12,25). These symptoms typically develop during the first 24 hours after rapid ascent, and this syndrome is known as Acute Mountain Sickness (AMS). The pathophysiology of AMS is largely unknown, although cerebral edema of vasogenic origin is thought to cause some of the predominant symptoms of AMS (e.g., headache, dizziness, and malaise) (13,25). Although not extensively studied, altitude exposure has been shown to have effects on cognitive performance (6,17,20,27) and affective mood states (1,23,24). For those who must work soon after ascent, the cognitive impairments and affective changes can degrade effectiveness (4). The exact relationship of these changes to AMS symptoms is not clear.

Although AMS is self-limited, it can be debilitating. Consequently, considerable interest exists in prophylactic measures. Acetazolamide has been widely used for pharmacologic prophylaxis (11), but recently dexamethasone has received attention as a potential prophylactic drug for AMS (16). Although studies have suggested dexamethasone may be effective in preventing AMS symptoms, its influence on cognitive performance and mood states has not been studied. Moreover, dexamethasone itself, a potent corticosteroid, has side effects (19) which might mimic the effects of altitude exposure.

The present study investigated the effects of dexamethasone and high terrestrial altitude on cognitive performance, affect, and personality traits. It was hypothesized that dexamethasone might decrease adverse effects in cognitive performance and mood associated with high altitude exposure.

MATERIAL AND METHODS

Sixteen healthy male volunteers from the U.S. Army participated in this study. They ranged in age from 19-26 years. Subjects were assigned at random to either a treatment (N=7) or a control group (N=9). At high altitude, one subject (control group) was removed from the study for medical evaluation, and his data were not used in analyses. All were life-long sea-level residents and had no exposure to altitudes greater than 1,000 m for at least 6 months prior to participation.

The study was conducted concomitantly with studies assessing the effects of dexamethasone on AMS symptoms and evaluating energy metabolism during exercise at altitude (21). The experiment was conducted as a double-blind, placebo controlled trial. Subjects in the treatment group received 4 mg dexamethasone by mouth every 6 h for 48 h at sea level (Natick, MA: 50 m), whereas the control group received identically appearing placebo. They were then transported from Natick to our Pikes Peak Laboratory Facility (Pikes Peak, CO: 4,300 m) in less than 6 h, where they remained for 6 days. They continued to take dexamethasone or placebo every 6 hours for 48 hours after their arrival at the peak, after which time both were discontinued. The subjects and overall

experimental design have been described in detail previously (21).

All dependent measures were administered as paper and pencil media except for the Clyde Mood Scale. It was administered with computer cards in a Q-sort format.

Cognitive performance was assessed by 5 timed tasks (addition, coding, computer interaction, pattern comparison and Tower of Hanoi). Sample items are shown in Figure 1. The computer interaction and Tower of Hanoi tasks were developed in our laboratory (2); the remaining tasks were similar to the tasks developed as part of the U.S. Navy's Performance Evaluation Tests for Environmental Research (PETER) program (5). All tasks stabilize with practice and are sensitive to altitude and a variety of other environmental stressors (4,15). These performance tasks require cognitive processes inherent in many real-world tasks (for a review see Jobe & Banderet (15)).

Training and practice with performance feedback were given on all cognitive tasks over a period of 16 days at sea level, with each task completed at least 17 times. Repeated testing procedures and methods were similar to those for the PETER program (4,5,15). The addition, coding, and pattern comparison tasks were given for four minutes each, the computer interaction task for seven minutes, and the Tower of Hanoi task for six minutes.

Affective mood states were assessed by means of the Clyde Mood Scale (8) and Multiple Affect Adjective Check List (MAACL). The Clyde Mood Scale consists of 48 adjectives, such as "kind,"

"alert," "lonely," self-rated on a four-point scale ("not at all," "a little," "quite a bit," and "extremely"). Prior analysis has shown that the 48 adjectives cluster into 6 principal mood factors -- friendliness, aggressiveness, clear thinking, sleepiness, unhappiness, and dizziness. Four of these moods are affected by high altitude (1,24). The Multiple Affect Adjective Check List (MAACL) (30) queried subjects about their moods at the time of the test. The MAACL consists of 132 adjectives such as "angry," "enthusiastic," and "worrying." A subject checks a box next to any of the words that apply to his current mood state. These adjectives cluster into 3 principal emotional factors -- anxiety, depression, and hostility. The MAACL has been used previously to measure moods at simulated high altitude (3).

Personality traits were measured using the Minnesota Multiphasic Personality Inventory (MMPI) (14). The MMPI was used to establish "before" and "after" values to determine whether subjects experienced any psychological effects from the administration and subsequent withdrawal of dexamethasone (9). The MMPI was administered 5 days prior to the first dosage of dexamethasone and again 7 days following withdrawal of the drug.

During days 2-5 at Pikes Peak, the subjects were tested at 0630, 1830, and 2200 h (dexamethasone was discontinued on Day 3). The Clyde Mood Scale and the MAACL were administered each evening at 2200 h, just before bed. The Tower of Hanoi task was given each evening at 1830 h. The 4 other cognitive tasks were administered at 0630 h each morning. On the day of ascent to the

peak, subjects arrived in mid-afternoon (1530-1630 h). The Tower of Hanoi task was therefore the first measure given (1830 h). The mood scales were given at 2200 h on this first day as well.

RESULTS

Data Analysis

A measure of cognitive performance, that is number of problems correct per minute, was derived to reflect the combined effects of changes in rate and accuracy (4). To penalize for guessing, this measure was decreased for the coding, pattern comparison, and Tower of Hanoi tasks, depending on the number of response alternatives.

Data from all cognitive tasks and the Clyde Mood Scale were submitted to two levels of statistical analysis. The first was a 2 (drug condition) X 4 (days) repeated-measures analysis of variance (ANOVA) with an average of the last two sea level days serving as the covariate because the two groups appeared different at sea level. Post-hoc comparisons were then performed to identify where differences occurred using Tukey's HSD test, controlling for the total number of means tested (18). The MAACL data was analyzed by three 2 (drug condition) X 6 (days) repeated measures ANOVAs, with the raw data for depression, anxiety, and hostility as dependent measures. Post hoc comparisons were performed using the Tukey test as described above. A significance level of $p \leq 0.05$ was chosen for all statistical tests.

Cognitive Performance

Mean scores for the cognitive tasks (number correct/minute) are shown in Figure 2. Dexamethasone-treated subjects

demonstrated superior performance on certain measures of cognitive performance at altitude. This finding was supported by significant main effects for dexamethasone for the computer interaction and addition tasks ($F(1,13) = 5.23, p < .04$; $F(1,13) = 4.72, p < .05$). It appeared that cessation of dexamethasone treatment had no effect on cognitive performance tests except possibly for the coding task where there was a significant interaction of dexamethasone and days at altitude ($F(3,42) = 3.31, p < .03$), but post-hoc comparisons revealed that there were no differences between the groups. The length of time at altitude appeared to affect cognitive performance independently of the dexamethasone effect. The computer interaction, addition, and Tower of Hanoi (possible and optimal) test scores changed over days at altitude, as was evidenced by a significant days effect ($F(3,42) = 4.38, p < .01$; $F(3,42) = 3.14, p < .04$; $F(3,42) = 6.99, p < .01$; $F(3,42) = 3.52, p < .03$).

Clyde Mood Scale

Measures of affective mood states were influenced by the combination of dexamethasone and altitude. The effects appeared to be most prominent during the initial exposure to altitude. Mean scores for the factors of the Clyde Mood Scale for sea level and altitude are shown in Figure 3. Altitude appeared to influence mood states as evidenced by a significant main effect of days. Friendliness, sleepiness, unhappiness, and dizziness scores changed over days, as evidenced by a significant days effect ($F(3,42) = 3.65, p < .02$; $F(3,42) = 5.97, p < .01$; $F(3,42) =$

4.81, $p < .01$; $F(3,42) = 11.25$, $p < .01$). There was no evidence for a significant main effect of dexamethasone on any of the factors, but there was a significant interaction of dexamethasone and altitude. Three of the six factors on this scale, friendliness, sleepiness, and dizziness, showed significant drug X day interactions ($F(3,42) = 2.91$, $p < .05$; $F(3,42) = 2.76$, $p < .05$; $F(3,42) = 9.60$, $p < .01$). Post-hoc comparisons revealed that subjects in the dexamethasone-treated group were less sleepy ($p < .05$) and dizzy ($p < .01$) than placebo-treated subjects on the first day of altitude exposure (Day 1). There was no difference between the friendliness scores on this day, however. In addition, the subjects in the dexamethasone-treated group did not show any mood changes when the treatment was discontinued after 3 days at altitude (Day 4).

Multiple Affect Adjective Check List (MAACL)

MAACL results appear to reflect similar findings to those noted on the Clyde Mood Scale, that is, dexamethasone appeared to influence mood scores during altitude exposure. Means scores for the factors of the MAACL for sea level and altitude are shown in Figure 4. Dexamethasone-treated subjects were less depressed than placebo-treated subjects on the first day at altitude (Day 1). This finding is supported by post-hoc analysis of the drug X days interaction ($F(5,70) = 2.84$, $p < .04$). Depression scores changed over days, as evidenced by a significant days effect ($F(5,70) = 5.73$, $p < .01$); however, the overall drug main effect was not significant.

Similarly, dexamethasone-treated subjects were less anxious than placebo-treated subjects on the first day at altitude (Day 1). This finding is also supported by the post hoc analysis of the significant drug X days interaction ($F(5,70) = 2.36, p < .05$). Anxiety scores changed over days, as evidenced by a significant days effect ($F(5,70) = 5.58, p < .01$). Again, the overall drug main effect was not significant.

No significant differences existed between the groups for hostility. Neither the drug main effect nor the drug X days interaction were significant. However, hostility levels did change over days, as evidenced by a significant days effect ($F(5,70) = 5.99, p < .01$).

No differences were found on any of the three measures for the MAACL after withdrawal of dexamethasone (Day 4).

Personality Traits

Interpretation of MMPI results revealed no abnormal trait scores either prior to the administration of dexamethasone or following its withdrawal.

DISCUSSION

The results of the present study demonstrate that dexamethasone can ameliorate the adverse effects of altitude exposure on certain measures of cognitive function and mood. Further, the results of the MMPI suggest that short-term dexamethasone administration and withdrawal in healthy subjects at altitude does not appear to have adverse effects on personality traits.

The finding of cognitive performance decrements and mood changes in untreated subjects during early altitude exposure is consistent with those seen in previous studies (1,3,4,24). However, in this study, as compared to a previous study using the same performance measures (4), only two of the five measures, computer interaction and addition, showed decrements in placebo subjects. One difference between the studies is the severity of altitude exposure (e.g., 4300 m altitude in this study vs 4600 m altitude in the previous study). Because performance impairments are positively correlated with altitude (3,4), one might expect fewer decrements in the present study. Another difference between the two studies is the schedule administration of the cognitive performance tasks. In the present study, four of the cognitive tasks were not administered until 15 hours after arrival at 4300 m altitude. The time course of decrements noted in the previous study suggests that all seven tasks were impaired after one to six hours, whereas only four were impaired after 14 to 19 hours (4). Therefore, cognitive performance in the present study may have been assessed too late to detect maximal altitude effects.

The questions of affective states and personality trait changes at altitude have not been extensively studied. Nelson (20) found changes in paranoid ideation, obsessive-compulsion and depression with altitude exposure on a climbing expedition on Denali (Mt McKinley) in Alaska. Similarly, Sharma and Malhotra (23) found changes in anxiety and depression with prolonged altitude exposure, and found differences between ethnic groups

undergoing the same altitude exposure. Similarly, we found that placebo-treated subjects were significantly more depressed and anxious than dexamethasone-treated subjects on the first day at altitude, as revealed by MAACL scores. However, we assessed MMPI traits before and after exposure to altitude, so these measures are not directly comparable with the previous studies. Further study is needed on this issue.

To the best of our knowledge, only two previous studies have looked at the effect of different pharmacologic prophylaxis strategies for AMS on cognitive performance. Carver and Winsmann (7) found no effect on cognitive performance as measured by responses to the Wonderlic Personnel Test at 3,950 m, and no effect of acetazolamide. White (28), on the other hand, found that acetazolamide appeared to sustain performance in two of six measures of cognitive performance in subjects traveling in the Peruvian Andes. Our results with dexamethasone were similar, in that it also prevented decrements in cognitive performance. That capability is admirable in a dangerous environment where unimpaired cognitive ability should have enhanced survival value.

Only one previous study at altitude has examined the effect of pharmacologic prophylaxis on mood (1). That study investigated acetazolamide plus staging and demonstrated absence of mood changes, although that study was not able to discern the independent effects of staging and acetazolamide individually. The results of the present study, performed in the same location as the staging and acetazolamide study, showed that dexamethasone

can prevent mood alterations in the absence of staging. We know of no previous studies of personality traits and AMS prophylaxis. Dexamethasone treatment by itself has an incidence of psychologic side effects (19), none of which were observed here. Cessation of dexamethasone therapy has also been associated with side effects (9), but, again, none were noted in this study which used healthy young subjects on a high dose for a relatively short period of time.

The effects of discontinuing dexamethasone, a powerful corticosteroid, is of concern in its potential use as an AMS prophylaxis due to its propensity for psychological and physiological withdrawal effects (9). As previously reported, clinical measures, but not ESQ scores, suggested the possibility of steroid withdrawal or, alternatively, recrudescence of AMS in our subjects after dexamethasone was discontinued at altitude (21). No similar effect was noted in cognition or mood states which were tested for 1-2 days after withdrawal, or for personality traits which were tested 7 days after withdrawal. If the symptoms were due to withdrawal, it is not clear from the data whether the effect represents physiologic or psychologic withdrawal. One recent study suggested the possibility of adrenal insufficiency following discontinuation of dexamethasone used for AMS prophylaxis (29). That study, which used an ad hoc questionnaire to elicit reports of symptoms, consistent with adrenal suppression and steroid withdrawal, provided no physiologic measures of adrenal suppression. Although withdrawal

effects from short-term steroid therapy are possible (26), another recent study failed to show adrenal suppression as measured by an ACTH stimulation test following exposure to a less intensive regimen of dexamethasone at a higher altitude (22). That result suggests the effect observed in the present study may not have been due to physiologic withdrawal. However, the present study also showed no evidence for psychologic dependence, at least not based on the parameters which were measured. This question is one that clearly needs further study.

Finally, another question of some interest is that of the relation of AMS symptoms and their influence on psychologic parameters measured here. The question is whether the symptoms of AMS cause the deficits noted in psychologic parameters, or are both symptoms and deficits related to a common condition, in this case most likely hypobaric hypoxia. There is no unequivocal way to tell from our present data; however, an earlier study showed a dissociation between the timecourses of AMS symptoms and cognitive performance (4). At high altitude, performance on many cognitive tasks had recovered to baseline values at times when AMS symptomatology was increasing or at maximum severity (4). Secondly, the recurrence of clinically obvious symptoms of either AMS or withdrawal (21) without deficits in measured psychologic parameters after dexamethasone had been discontinued suggests the two are not causally related. This question is one that deserves more attention, but may be difficult to adequately assess.

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Figure Captions

1. Samples of 5 cognitive performance tests used in this study.
Coding, addition, pattern comparison, Tower of Hanoi, and computer interaction.
2. Cognitive performance on the 5 performance tests on the last two days (averaged) at sea level and 4 days at altitude.
3. Performance on the Clyde Mood Scale on the last two days (averaged) at sea level and 4 days at altitude.
4. Performance on the Multiple Affect Adjective Check List on the last two days (averaged) at sea level and 4 days at altitude.

Footnotes

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Disclaimer

Human subjects participated in these studies after giving their free and informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC Regulation 70-25 on Use of volunteers in research. The views, opinions, and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation.

The image is a 2x2 grid of four panels, each containing a different type of visual information:

- Top-Left Panel:** Contains the title "CODING" and two lines of text. The first line is "NUMBER: 1 2 3 4 5 6 7 8 9" and the second line is "SYMBOL: = U X O L I > ~ /". Below these is a sequence of numbers and parentheses: "4 1 2 4 1 2 6 4 5 6" and "() () () () () () () () () ()".
- Top-Right Panel:** Contains the title "ADDITION" and a table of numbers. The table has three columns of numbers: 71, 20, 53; 19, 51, 33; 76, 40, 67. Below the table is a row of dashes: "----".
- Bottom-Left Panel:** Contains the title "PATTERN COMPARISON" and a diagram of a pattern. The pattern consists of a grid of asterisks (*) and dashes (-) arranged in a specific shape.
- Bottom-Right Panel:** Contains the title "COMPUTER INTERACTION" and a list of arithmetic problems: "73374 MINUS 30776.9 =", "58.65 PERCENT OF 41930.9 =", "7398.99 DIVIDED BY 54.88 =", "8897 PLUS 69194765 =", and "4590.84 MULTIPLIED BY 271.1 =".

NUMBER: 1 2 3 4 5 6 7 8 9
SYMBOL: = U X O L] > - /

71	20	27	53	20
19	51	83	33	35
76	40	47	67	11

Age Group	No	Somewhat	A lot	A great deal
18-24	~45%	~35%	~15%	0%
25-34	~35%	~40%	~20%	0%
35-44	~25%	~45%	~25%	0%
45-54	~15%	~40%	~35%	0%
55-64	~10%	~35%	~40%	~15%
65+	~5%	~30%	~45%	~20%

POSSIBLE? YES, NO
OPTIMAL? YES, NO

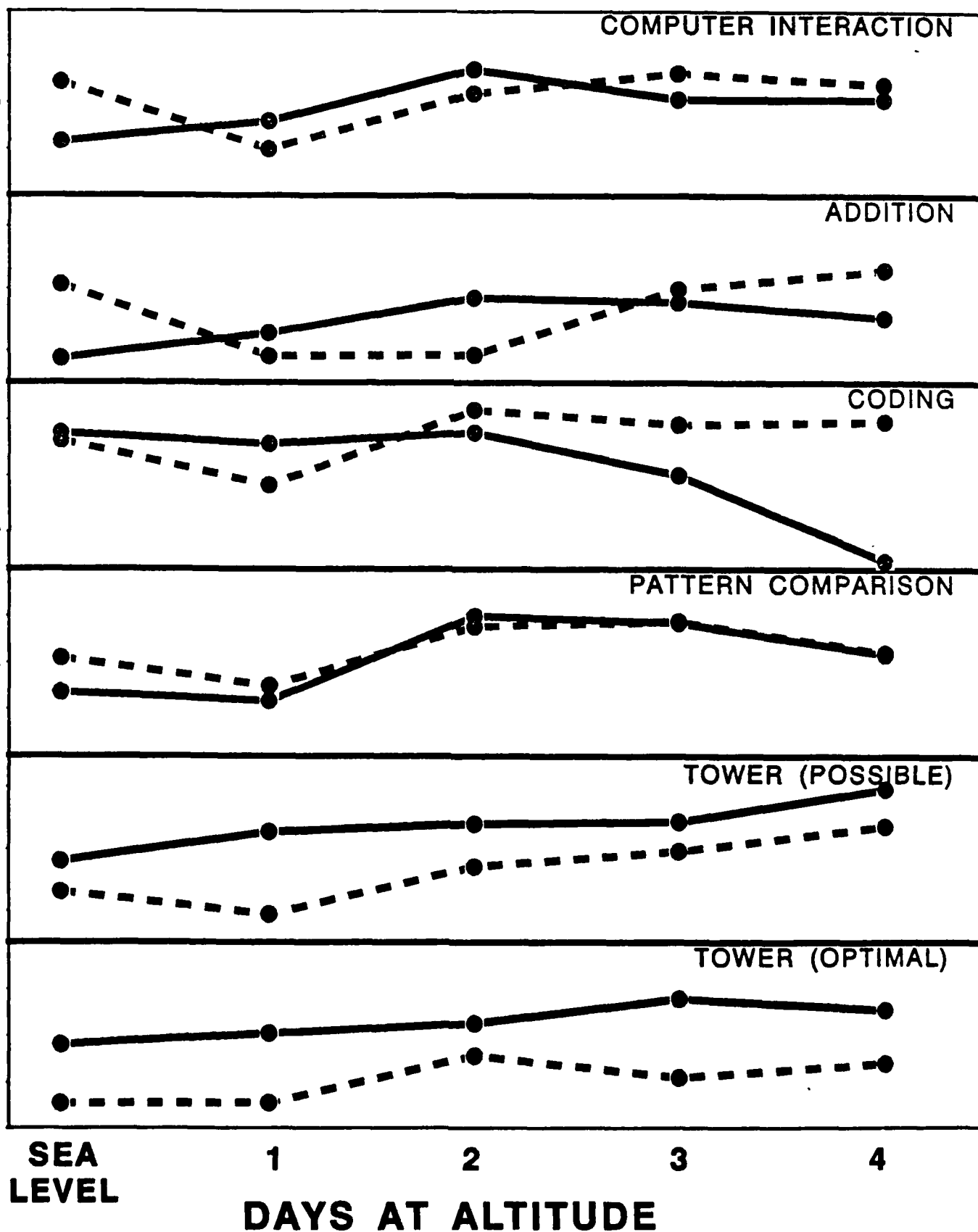
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COGNITIVE PERFORMANCE

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DEX —

MEAN NUMBER CORRECT PER MINUTE

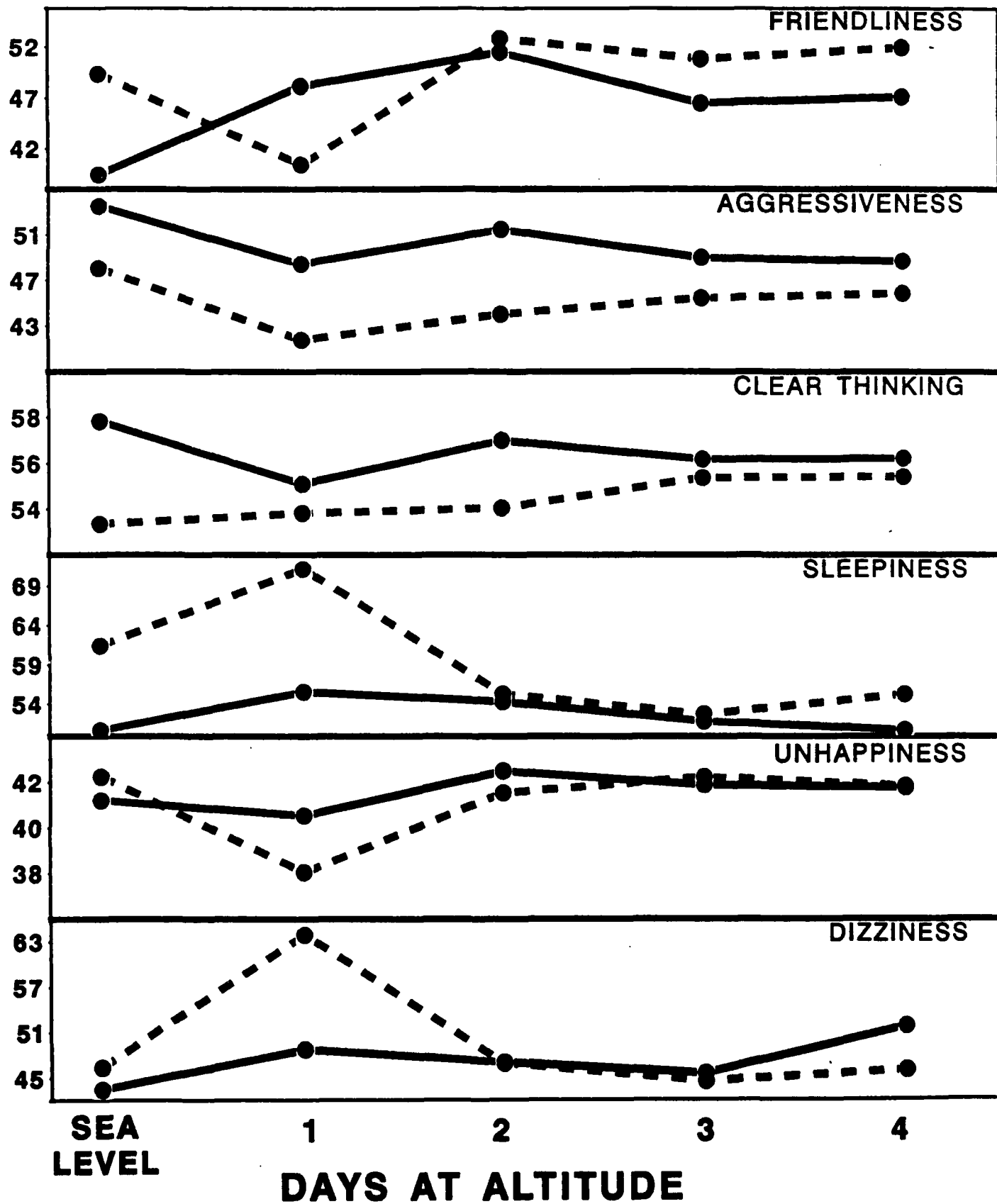


CLYDE MOOD SCALE

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DEX —

MEAN MOOD FACTOR SCORE



MULTIPLE AFFECT ADJECTIVE CHECK LIST

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DEX —

